NanoCalibur

The Scalable Nanoparticle Synthesis System Lab-scale discovery and preclinical to GMP manufacturing



NanoCalibur[®]

NanoCalibur™ Technologies

NanoCalibur[™] provides unprecedented solutions with advanced microfluidic technologies to formulate various types of NPs with precisely defined properties and tunable scalability.

Microvortex mixing patterns engineered to formulate nanoparticles

• These scalable single cartridge units meet a range of throughputs from discovery to preclinical studies with > 95% mixing efficiency for uniform synthesis.

Dean vortex-induced mixing of MPA126



capacity in response to market needs.



PMS-cMPA126 X16 NanoCalibur™ GMP

Swirling vortex-induced mixing of SMR25T







PMS-cSMR25 T16 NanoCalibur™ GMP



Synthesis chip parallelization for scalable production

• Microfluidic parallelization preserves the microfluidic pattern of one unit of micromixer and minimizes optimization time in the process of scaling up to mass production with rapid adjustments in production

• The controlled environment of microfluidic systems reduces variability, leading to more consistent and reproducible outcomes in LNP production and meeting the regulatory compliance for product consistency.

• NanoCalibur™ utilizes a network of MPA126 X1 to distribute the precursor solutions in PMS-cMPA126 and ensure that shear stress remains within critical levels that preserve mRNA integrity.

Product Line

NanoCalibur™ Lab	NanoCalibur™ GMP	NanoCalibur™ Commercial
Small-scale synthesis for discovery and preclinical	GMP level production for preclinical and clinical	GMP to Commercial
2.5 - 20 mL/min (0.15 - 1 L/h)	2 - 6 L/h	6 - 20 up to 80 L/h (with 4 PMS cartridges)



• NanoCalibur™ operates for all the production rates under controlled shear rates at which the produced LNPs are stable and uniform with intact mRNA encapsulated. Other microfluidic syntheses (circle) result in

high variability of the size or excessive aggregation of precursors in a lower shear rate, or reportedly cause the decrease in biomolecular stability, possibly leading to loss of therapeutic reagents.

LNP Production Under Controlled Shear Rates Prevents RNA Damages

Microfluidic parallelization minimizes the shear stress exposed to the precursor components

- Shear rates involved in microfluidic mixing at high flow rates reportedly cause the decrease in biomolecular stability, possibly leading to loss of therapeutic reagents such as damaged mRNA.
- NanoCalibur™ distributes the flow of lipid and mRNA solutions across multiple pathways and ensures that shear stress applied to mRNA remains within critical levels that preserve mRNA integrity.

High stability of mRNA under a suitable shear rate mediated mRNA-LNP synthesis

- Cells treated with mCherry LNPs prepared at $0.3 \times 10^5 \text{ s}^{-1}$ exhibited significantly higher mCherry expression compared to those treated with mCherry LNPs prepared at 3.0×10^5 s⁻¹, although the encapsulation efficiency of mRNA-LNPs for both cases of the shear rates remains the same (approximately 95%).
- While shear rates do not significantly alter the physicochemical properties of LNPs and the encapsulation efficiency remains similar under both high and low shear rate conditions, the excessive shear stress during LNP formulation causes mRNA damage and results in significant differences in protein expression.



NanoCalibur[™] Lab

The system offers a user-friendly operation, making lab-scale synthesis and the development of new drug-loaded nanoparticles more accessible. It supports production rates ranging from 2.5 to 20 mL/min (0.15 to 1 L/h).

1 Closed-loop feedback control system and computerized manufacturing

- High-precision flow control by closed-loop pressure regulation for robust manufacturing.
- The continuous feedback loop implemented into the microfluidic synthesis chip facilitates immediate responses to any fluctuations that may affect the produced LNP quality.



2 User-friendly precursor preparation

• Automated operation with no syringe or tubing bundles makes it easier to reliably use for small-scale nanoparticle synthesis.





6 Product tube multi-holder for multiple syntheses

- Rotatable multi-holder system
- · Autonomously designed series of synthesis conditions

3 Synthesis cartridge made of stainless steel (SUS 316L)

• Semi-permanent use and cost-effective synthesis with no laborious replacement of chips

* Disposable plastic cartridge available (Optional)

4 Cartridge cleaning protocol

6

Cleaning protocols prepared before and after synthesis

Start Nan	oCalibur⁼	[™] cleaning
	Highly recom Prepare 10 m in each tube	mended L of 100% ethanol for cleaning
Open Door	Back	Next

5 Touchscreen display

• User-friendly interface for setting the condition and monitoring the progress

- * Optimized conditions indicated in Library:
- FRR (Flow Rate Ratio) = 1:5.5
- TFR (Total Flow Rate) = 5.2, 10.4, 19.8 mL/min

	01 May., 2024	
Air pressure 🌒 Door 🌒	Condition 3	
	Total flow rate	5 mL/min
۵	Flow rate ratio	5:1
100 100 50 0	Product volume	3 mL
	Waste	0.3 mL
		Stop

NanoCalibur™ GMP

A robust nanoparticle production system with integrated synthesis and cleaning processes supports from preclinical animal studies to clinical trials.

1 Precise flow control by integrated mass flow controller (MFC)

- The continuous feedback loop integrated into the microfluidic system ensures that synthesis conditions remain optimal throughout the manufacturing process.
- Enhanced control allows for real-time monitoring and adjustment of flow conditions, facilitating immediate responses to any fluctuations that may affect the product quality.



2 Durable precursor containers for large-scale LNP production

• Maximum pressure of up to 7 bar (101.5 psi) applicable with stainless steel (SUS 316L)





③ Other features of NanoCalibur™ GMP

- Ensuring stable productivity at a liters-per-hour scale through high precision flow control and PMS based synthetic cartridges
- Clean in place (CIP), without relocation or disassembly, to ensure GMP compliance with product quality standards

6 Network

 Built-in Wi-Fi and Ethernet network for seamless data export and firmware upgrades at no additional cost

Synthesis cartridge made of stainless steel (SUS 316L)

• Semi-permanent use and cost-effective synthesis with no laborious replacement of chips

* Disposable plastic cartridge available (Optional)



5 Logs and user control

Save all processes as document recordsUser-specific administrative records

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Case Studies

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LNP



Uniform and size-controllable production of mRNA-LNPs and ASO-LNPs

- The size of LNP is varied with the total flow rate under shear rates below 1×10^5 s⁻¹, and the payload is encapsulated with > 90% efficiency in all LNPs.
- Uniform LNPs with an encapsulation efficiency of > 90% are produced by MPA126 X1.

Highly stable payload encapsulation

• Both the size and encapsulation efficiency of LNPs synthesized with a high mixing efficiency of > 95%are maintained for 4 weeks.

60-0.3 60size В 40 0.2 40 Me 20 20-0 2.6 5.2 10 20 2.6 5.2 10 20 Total flow rate (mL/min) Total flow rate (mL/min) 120 0.5 0.4 80 ê 90 -0.3 60 В o9 Size 0.2 40-Mean 30 20 - 0.1 LNP 3 LNP 1 LNP 2 LNP 3 LNP 1 LNP 2 - mCherry - Cas9 - ASO 150 1.0 (100 0.8 size 0.6 g 804

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80





Uniform liposome production

• Liposomes synthesized by MPA126 X1 exhibit a PDI of less than 0.2, demonstrating excellent uniformity.



21 28

Time (d)

0.2

0.0

0 7 14

Time (d)

21 28

[1] Jung, Sungjin, et al. Advanced healthcare materials 9.22 (2020): 2001633. [2] Toth, Michael J., et al. Lab on a Chip 17.16 (2017): 2805-2813. [3] Kim, YongTae, et al. Nano letters 12.7 (2012): 3587-3591. [4] Mieszawska, Aneta J., et al. Bioconjugate chemistry 24.9 (2013): 1429-1434.

0 7 14

Lipid-Polymer



Production of uniformly sized lipid-polymer NPs

• The NPs produced by SMR25 T1 showed a higher size uniformity than the NPs produced by conventional synthesis.

Production of drug-loaded lipid-polymer NPs

- NPs manufacturing technology that enables the production of highly uniform NPs with high drug encapsulation efficiency.
- The NPs produced by SMR25 T1 showed a higher cellular internalization efficiency and anti-tumor effect than the NPs produced by conventional synthesis.
- Efficient NPs mass production through an optimized synthesis system built based on microfluidic technology.



Lipid-Protein





Uniform lipid-protein production

• Both size and uniformity (PDI) of lipid-protein synthesized through high mixing efficiency of MPA126X1 are maintained for 3 months.









NanoCalibur™ Products

Sales and Service



Sales of the instruments



Sales of the semi-permanent cartridges (MPA126 X, SMR25 T, and the PMS)



Optimal synthesis conditions of representative NPs provided and updated



Prospective Clients



NanoCalibur™ Lab

Research laboratories and academic institutions that are developing nanoparticle-based vaccine and therapeutics.



NanoCalibur[™] GMP & Commercial

GMP manufacturers that require large-scale production for preclinical studies, clinical trials, and commercial processes.

Nanoparticle Formulation Service

LNP formulation service



Polymeric nanoparticle formulation service





Specifications

NanoCalibur™ Lab

Droccuro	Operation pressure		4 bar	
riessure	Flow control resolution		0.1 mL/min	
	Total flow rate		2.5 - 20 mL/min	
Throughput			0.15 - 1 L/h	
	Product per run		3 - 90 mL	
		Aqueous phase	50 mL	
Container	(Conical tube)	Organic phase	50 mL	
	Product container (Conical tube)	Product & waste	15 mL	
	Dimension (W x L x H)	32 cm x 32 cm x 31 cm	
General	Weight		Total: 27 kg (Instrument: 25 kg, Display: 2 kg)	
specification	Supply voltage		AC 100 V - 240 V	
	Power consumption		Max. 230 W	
Formulation information of precursors	Total lipid concentration		0.6 - 13 mg/mL	
	Nucleic acid concentration		0.004 - 0.3 mg/mL	
	Minimum amount of initial mRNA		0.007 mg	
Encapsulation efficiency		> 90 %		

Cartridge MPA126 X1, SMR25 T1

	Diameter	100 mm
General specification	Weight	< 1 kg
	Main component	SUS 316L Stainless steel for semi-permanent use



NanoCalibur™ GMP

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Max. pressure 7 bar	
30 - 100 mL/min	
2 - 6 L/h	
Precursor container Organic 1 L, 2 L	
(Stainless steel) Aqueous 5 L, 10 L phase	
ContainerPrecursor housing holder [Dimension (W x L x H)]24 cm x 46 cm x 30 cm	
Product container (Disposable storage Product 5 L, 10 L bag)	
Dimension (W x L x H) Instrument 44 cm x 44 cm x 28 cm	
Instrument 44 kg	
Precursor housing holder 5 kg	
pecification Precursor Organic (1 L) 4 kg	
containers Aqueous (5 L) 9 kg	
Supply voltage AC 100 V - 240 V, 50/60 Hz	
Power consumption 130 W	

Cartridge PMS-cMPA126 X16, PMS-cSMR25 T16

General pecification	Diameter	160 mm
	Weight	< 10 kg
	Main component	SUS 316L





PMS-cMPA126 X16

PMS-cSMR25 T16

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6L Stainless steel for semi-permanent use





MEPSGEN, 7F, Hanyang Tower, 12, Beobwon-ro-11-gil, Songpa-gu, Seoul, Republic of Korea Tel +82-2-401-4370 | Fax +82-2-400-4855 www.mepsgen.com